REMARKS

Reconsideration of the present application is respectfully requested.

Status of the Claims

Claims 152 to 170 have been acted upon by the Examiner. Claim 163 has been amended. No claims have canceled or added. Accordingly, Claims 152 to 170 are presented for examination.

Claim Objection

Claim 163 is objected to because it depends from itself. Applicants have amended claim 163 to depend from 162; accordingly, this objection should be withdrawn.

Obviousness Rejections

All previously pending obviousness rejections that relied on the combination of Goodey *et al.* (WO 97/31947) and Matsuoka-1 *et al.* (EP 0 428 758) as evidenced by Cohn *et al.* (J. Am Chem. Soc., vol. 68, pp. 459-75, 1946), Shaklai *et al.* (J. Biol. Chem., vol. 259, pp. 3812-17) and Ohmura *et al.* (EP 0 570 916 A2) have been withdrawn.

Claims 152, 154-162 and 164-170 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goodey *et al.* (WO 97/31947) and Johnson *et al.* (U.S. Patent No. 5,625,041). Claims 153 and 163 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Goodey *et al.* and Johnson *et al.* as applied to claim 152 and further in view of Fisher *et al.* (U.S. Patent No. 4,228,154).

The Examiner alleges that it would have been obvious for one of skill in the art to add the negative mode cation exchange (CE) and anion exchange (AE) steps of Johnson *et al.*'s methods to the method of Goodey *et al.* The Examiner alleges that the motivation for this combination is that Goodey *et al.* teaches the use of dyes in albumin purification, whereas Johnson *et al.* teaches ion exchange run in the negative mode with respect to albumin to remove such dyes as used in protein purification processes.

"To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143. Here, there is no suggestion or motivation to combine the references, and the references when combined do not teach or suggest all the claim limitations.

A. There is no motivation to combine Goodey *et al.* and Johnson *et al.*

"Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so." M.P.E.P. § 2143.01. While the Supreme Court's recent decision in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, (2007) cautioned against applying the teaching, suggestion, motivation test in a rigid manner, one of skill in the art must still see a *benefit* in combining the references. *Id.* ("The proper question to have asked was whether [one] of ordinary skill, facing the wide range of

needs created by developments in the field of endeavor, would have seen a *benefit* to [combining the references.]") (emphasis added). Here, there is no such benefit.

The basis of the Examiner's motivation for combining Goodey *et al.* and Johnson *et al.* is said to be that the reader of Johnson *et al.* would have known that an ion exchange step run in the negative mode with respect to albumin could be used to remove dyes which are used in the process of protein purification whereas Goodey *et al.* teaches the use of such dyes in albumin purification. As explained below, this rejection is without basis because one of skill in the art would not add the negative ion exchange step of Johnson *et al.* because Goodey *et al.* already addresses the problem for which the negative ion exchange step is used in Johnson *et al.*

"The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P. § 2143.01. Here, there is no such desirability as Goodey *et al.* addresses the problem that the negative ion exchange step of Johnson *et al.* is designed to address. It is only by using knowledge gleaned from applicants' disclosure that one of skill in the art would be motivated to combine these references. This, however, cannot be the basis for a *prima facie* case of obviousness. M.P.E.P. § 2145.

According to the Examiner's argument, one of skill in the art would recognize that the Goodey *et al.* process would result in an albumin product that possessed undesirable levels of dye leachate such that the product would benefit from the removal of dye leachate using the negative ion exchange step of Johnson *et al.* However, this is not the case. To the contrary, Goodey *et al.* expressly teaches that its method already addresses the issue of unacceptable levels of leached dyes.

For example, on page 22, lines 6-12, Goodey *et al.* teaches that the selection of a specific dye, Delta Blue Agarose, "*has been found to reduce the levels of blue leachates generated by the matrix*" (emphasis added) and that the selection of a specific spacer, 1,4-diaminobutane, provides optimal spacer length with respect to eluate albumin purity. Goodey *et al.* tells its readers to optimise its dye affinity chromatography step by ensuring that "*[t]he aminobutyl-Reactive Blue 2 is prepared to a minimum purity of 98% total peak area as determined by analytical HPLC*" (page 22, lines 25-26).

Goodey *et al.* typically immediately follows the dye affinity chromatography step with ultrafiltration and gel permeation steps (see Goodey *et al.*, page 23, line 7 to page 24, line 18; page 26, lines 1-3; page 33, lines 20-22; and page 34, lines 1-3). Goodey *et al.* does not teach a method that relies on any ion exchange step run in the negative mode with respect to albumin. subsequent to its dye affinity chromatography step. Yet, Goodey *et al.* teaches the reader that its method produces albumin of satisfactorily high purity (see Goodey *et al.*, page 5, lines 16-28; and page Example 9 on page 39 *et seq*). Thus, the reader of Goodey *et al.* expects to be able to use its method to produce albumin having an acceptable level of purity, with inconsequential levels of dye leachates and without using a negative ion exchange step.

Thus, Goodey *et al.* teaches that the problem of dye leaching, as reported in the prior art (for example, in Johnson *et al.*), has been adequately addressed in Goodey *et al.* by the selection of a suitable dye and spacer and the use of suitably pure dyes in the preparation of the affinity column. Consequently, one of skill in the art after reading Goodey *et al.* would not be concerned about levels of dye leachate in the albumin product that results from the use of the method of Goodey *et al.* Consequently, one of skill in the art would have no reason to consult Johnson *et al.*, much less see the *benefit* in adding the negative ion exchange step of Johnson *et al.* to

the method of Goodey *et al.* *See KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct.1727, (2007).

Accordingly, it will be clear to the examiner that the combination of Goodey *et al.* and Johnson *et al.* is improper.

B. The combination of Goodey *et al.* and Johnson *et al.* does not teach or suggest all of the claim limitations of the pending claims

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). M.P.E.P. § 2143.03.

1. The combination does not teach a negative CE step

As discussed above, there is no teaching, suggestion, or motivation to combine Goodey *et al.* and Johnson *et al.* nor would one of skill in the art recognize a benefit of combining Goodey *et al.* and Johnson *et al.*

However, even if the references were combined as suggested by the Examiner – which would be improper – the combination would *not* result in the claimed invention. Each of the independent claims recites a CE step run in the negative mode with respect to albumin. The combination suggested by the Examiner would result in the addition of a negative AE step from Johnson *et al.* to the method of Goodey *et al.*

Johnson *et al.* clearly teaches that an AE or CE step (not both) should be selected to remove dye leachate, and that the decision to use one or the other is

determined by the nature of the dye compound to be removed. Please see Johnson *et al.*, col. 2, lines 37-40, which states that

> These dye compounds are usually anionic, in which case an anion-exchanger is most appropriate in the process of the invention, but some are cationic, in which case a cation-exchanger is most appropriate.

As discussed above, Goodey *et al.* clearly teaches that a specific dye, Delta Blue Agarose, is preferred (see page 22, lines 6-12). Delta Blue Agarose is an anionic dye. Goodey *et al.* also mentions other (less preferred) dyes.

> The affinity matrix may comprise any Cibacron Blue type of dye which binds albumin, for example Reactive Blue 2, Procion Blue HB, Blue Sepharose, Blue Trisacryl and other anthraquinone-type compounds. (page 22, lines 3-5).

All of these dyes are said by above-quoted passage of Goodey *et al.* to be Cibacron Blue type dyes. Cibacron Blue dye is an anionic dye that is suitably removed by an anion exchanger step. This is evidenced by the disclosure in Example 1 of Johnson *et al.*, which reports that Dowex-1 resin (a strong base anion exchange resin – see attached datasheet from the manufacturer) could be used to separate human serum albumin from Cibacron Blue dye covalently attached to a spacer.

Thus, even if the reader of Goodey *et al.* did seek guidance from Johnson *et al.* for the modification of *Goodey et al.'s* method so introduce a further step to remove the anionic dyes taught in Goodey *et al.* from its albumin product, then it is clear the that skilled person would do so by the selection of an anion exchange step that is run in the negative mode with respect to albumin.

Accordingly, the combination of Goodey *et al.* and Johnson *et al.*, for the reasons suggested by the Examiner (i.e. to improve Goodey *et al.'s* method to remove any leaked dye) would not result in a process employing a negative mode CE step.

Accordingly, the combination of Goodey *et al.* and Johnson *et al.* would not result in the claimed process.

2. The combination does not teach a negative mode CE step loading concentration of 10-250 $g.L^{-1}$

The claims of the present application recite that the albumin solution that is applied to the cation exchange step that is run in the negative mode with respect to albumin has an albumin concentration of 10-250 $g.L^{-1}$.

The Examiner contends that Goodey *et al.* teaches a process for purifying albumin solutions wherein, *inter alia*, the albumin solution that is subjected to the cation exchange step that is run in the negative mode with respect to albumin has an albumin concentration of 10-250 $g.L^{-1}$. Applicants submit respectfully that this reading of Goodey *et al.* is incorrect.

The Examiner has already correctly acknowledged that Goodey *et al.* does not teach a CE step that is run in the negative mode with respect to albumin (for example see the statement on page 7, part (B) of the current office action). Since Goodey *et al.* does not teach a CE step that is run in the negative mode with respect to albumin, it clearly cannot teach any specific loading conditions with respect to such step.

Rather, the Examiner's citations on page 5, second paragraph, of the current office action relate to passages in Goodey *et al.* that teach either (1) preferred relative amounts of albumin to chromatography matrix in positive mode CE and AE, and PBA chromatography, steps; or (2) the use of ultrafiltration to manipulate albumin concentrations.

Applicants address each of the passages of Goodey *et al.* that have been cited by the Examiner in turn.

- *Page 21, line 8 & page 32, lines 10 and 25* – teach relative ratios of weight of albumin not absolute albumin concentration as in the claims.

  These passages specify that a CE or AE column used in the positive mode with respect to albumin can be loaded with albumin that is 1-50 g albumin/L matrix. This defines the weight of albumin in grams loaded per liter of matrix in the column. This unit is not an absolute concentration of albumin. Rather, this defines the relative ratios of weight of albumin to volume of matrix not an absolute albumin concentration of 1-50 $g.L^{-1}$. Accordingly, this disclosure does not teach or suggest any particular absolute albumin concentration. In any case, these relate to the loading conditions for positive mode ion exchange steps, not a negative CE step as defined by the present claims.

- *Page 23, line 25 & page 24, line 23* – teach concentrations of albumin produced by an ultrafiltration step not loading concentrations as in the claims.

  These passages relate to a concentration of albumin that can be produced using an ultrafiltration step. Both ultrafiltration steps come after the positive mode CE step defined by Goodey *et al.* There is no suggestion in Goodey *et al.* that the defined concentrations are in any way relevant to the selection of an appropriate loading concentration for a CE step at all, much less a CE step that is run in the negative mode with respect to albumin.

- *Page 33, line 21 & Page 39, line 9* – teach concentrations of albumin produced by an ultrafiltration step not loading concentrations as in the claims.

  These passages relate to the concentration of albumin that can be obtained after an ultrafiltration step that is performed on the eluate that results from a Delta Blue Agarose dye affinity chromatography step. There is no suggestion in Goodey *et al.* that the defined concentrations

> are in any way relevant to the selection of an appropriate loading concentration for a CE step at all, much less a CE step that is run in the negative mode with respect to albumin. In the passage at page 39, line 9, the thus concentrated albumin is subjected to PBA chromatography and then gel permeation. Neither of PBA chromatography or gel permeation are the same as an ion exchange step.

- *Page 37, line 10* – teaches relative ratios of weight of albumin for loading a PBA chromatography step not absolute albumin concentrations for a negative ion exchange step as in the claims.

> This passage refers to loading conditions for a chromatography step (here, a PBA chromatography step, which is not even an ion exchange step) defined by the unit "g albumin/L matrix". As explained above, this is a measure of the relative amounts of albumin versus matrix and it is not the same as absolute albumin concentrations. In any case, this relates to PBA chromatography and it is not relevant to a CE step at all, much less a CE step that is run in the negative mode with respect to albumin.

Accordingly, it is clear that none of the cited passages teach loading a CE step that is run in the negative mode with respect to albumin with an albumin solution that has an absolute albumin concentration of 10-250g.L^{-1}.

According to the Examiner, the claims are obvious if one modifies the method of Goodey *et al.* by adding the negative mode ion exchange step of Johnson *et al.* Yet, the Examiner has not identified any passage in either of these documents that would provide reason for the skilled person to select an albumin concentration of 10-250 g.L^{-1} for loading onto a negative mode CE step.

To the contrary, neither Goodey *et al.* or Johnson *et al.* teach or suggest that albumin should be loaded onto a negative mode CE step at a concentration of 10-250 g.L^{-1}. In fact, Johnson *et al.* is totally silent on the concentration of albumin to be

loaded onto any ion exchange step, much less a cation exchange column that is run in the negative mode with respect to albumin. Likewise, there is no specific guidance in Goodey *et al.* to result in the skilled person being specifically motivated to apply an albumin solution having an albumin concentration of 10-250 $g.L^{-1}$ to a negative mode ion exchange step.

Accordingly, it follows that, even if Goodey *et al.* and Johnson *et al.* were combined in such a way that makes it obvious to apply a negative mode CE step to the method of Goodey *et al.* (for which we see no justification) then, nevertheless, there is still no suggestion that albumin should be presented at a concentration of 10-250 $g.L^{-1}$ for a negative mode CE step.

Accordingly, this further shows that the combination of Goodey *et al.* and Johnson *et al.* does not teach the claimed process.

Given the above, Goodey *et al.* and Johnson *et al.* do not render Claims 152, 154-162 and 164-170 obvious. Similarly, because the rejection of Claims 153 and 163 are based on the underlying rejection of Claim 152, Goodey *et al.* and Johnson *et al.* in further view of Fisher *et al.* do no render Claims 153 and 163 obvious. Accordingly, the Examiner's Section 103 rejection of Claims 152 to 170 should be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, applicants assert that the claims are in condition for allowance, and request respectfully issuance of a Notice of Allowance. If there are any issues remaining, applicants request an interview prior to

the issuance of an action. If any additional fees are required to continue the prosecution of this application, please charge such fees to Deposit Account 19-5425.

Respectfully submitted,

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